EXHIBIT A

Guidance for Industry and FDA

Medical Glove Guidance Manual

Draft Guidance – Not for Implementation

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Small Manufacturers Assistance
Office of Health and Industry Programs

4 GLOVE LUBRICANTS

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RELEASE AGENTS

Natural rubber latex and some synthetic polymers are tacky, and gloves made of these materials stick to the mold, commonly called a former. Therefore, a mold-release agent or lubricant such as calcium carbonate or a mixture of calcium carbonate and cornstarch is used. A small amount of the release agent remains on the "inside" surface of the glove. In some processes, most of the mold release agent is removed from the surface of the glove by washing or treating with acid.

POWDERED GLOVES

During processing, the "outside" of the gloves are coated with a donning lubricant. In most glove manufacturing processes, gloves are inverted when they are stripped from the formers. For most powdered gloves, the "outside" lubricant is cornstarch which remains, after stripping, inside the inverted gloves as the donning lubricant or powder.

Donning lubricants such as cornstarch, silicone, etc., are used to ease insertion of the user's hand into a glove. Powdered lubricants are also called donning powders or dusting powders. Cornstarch which meets the specification for absorbable donning or dusting powder in the United States Pharmacopeia (U.S.P.) is a commonly used lubricant for patient examination gloves.

Powder used for lubricating examination gloves should meet the U.S.P. monograph for absorbable dusting powder or be shown to be equivalent in terms of safety and effectiveness. The *U.S.P. NF XVII Monograph for Absorbable Dusting Powder* is presented near the end of this chapter. The 510(k) submission must state the type, specifications and source of powder or other donning lubricant used on the gloves. Talc, cotton flock, and other non-absorbable materials are **not** acceptable as a lubricating, dusting or donning powder. Lycopodium (club moss spores) and ground pine pollen are toxic and are not acceptable as powder on or in medical gloves. Also, the ASTM standards require that the inside and outside surface of medical gloves be free of talc (paragraph 4.3 of D 3578-91 and D 5250-92, and paragraph 5.3 of D 3577). The ASTM standard for finger cots (paragraph 5.3, D 3772) requires that cots

and any dressing materials applied to them not liberate substances known to be toxic or otherwise harmful under normal conditions of use.

Absorbable dusting powder **for lubricating a surgeon's glove** is a transitional device (a device formerly regulated as a new drug before 1976) and is listed under 21 CFR 878.4480 as a Class III device which requires an approved Premarket Approval Application (PMA) or prior to May 28, 1976, a New Drug Application (NDA). Only absorbable dusting powders from powder manufacturers that have an approved PMA or NDA may be used on powdered surgeon's gloves.

A small amount of silicone or other lubricant is used on some powder-free gloves to aid in donning. If used, such lubricants should be on the finished gloves when biocompatibility tests are conducted. The exact composition of the lubricant should be identified in the 510(k) submission.

Powder from medical gloves directly contacts wounds, body cavities and skin, and it contaminates the user environment. Due to the enormous numbers of medical gloves used in healthcare, the amount of powder on finished gloves needs to be minimized. To meet QS requirements for device specifications in §§820.30 and 820.181, manufacturers should establish a specification for the amount of powder on a glove. (Also see the labeling information in chapter 6 regarding the powder level on gloves.) The manufacturer should also establish a procedure to verify that the powder level on the finished gloves meet their specification.

CONTENT AND FORMAT OF PMAS FOR ABSORBABLE DUSTING POWDER FOR SURGICAL GLOVES

Prior to the passage of the Medical Device Amendments to the Food, Drug and Cosmetic Act (FD&C Act) on May 28, 1976, absorbable dusting powder for surgical gloves was regulated as a drug and required an approved New Drug Application (NDA) before it could be marketed in the United States (Federal Register, May 25, 1971). Therefore, under the Medical Device Amendments to the FD&C Act, such dusting powder was automatically classified as a Class III, transitional device. The final classification for this device was published in the Federal Register, June 24, 1988, Vol. 53, No. 122, page 23875, and listed in 21 CFR 878.4480. In this final ruling, absorbable powder for lubricating a surgical glove is defined as a powder made from corn starch that meets the specifications for absorbable powder in the United States Pharmacopeia (U.S.P.) and that is intended to be used to lubricate the hand in order to ease the donning of surgical gloves. The device is absorbable through biological degradation. Since this final ruling has placed this device in Class III, all new dusting powder for use with surgical gloves must be approved for marketing by the PMA process (21 CFR 814).

The Infection Control Devices Branch may be consulted prior to the initiation of any tests or during the preparation of an application for absorbable dusting powder for surgical gloves to discuss protocols and data requirements.

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experimental methods, controls), observations, statistical analyses, conclusions and comments. Additional specific directions on protocols are addressed in other sections of this guidance document.

2. Analytical methods must be clearly described and conform to recognized analytical and statistical methods.

G. Physical and Chemical Information

1. Manufacturing (21 CFR 814.20(b)(4)(v))

The sponsor should submit a complete description of the methods, facilities, and controls used in the manufacture, processing, packing, and storage of the device. The description should contain sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgement about the quality control used in the manufacturing of the device. This information should begin with the origin of the raw material and should detail all manufacturing processes through the distribution of the finished product. The source of and technical information for each reagent used in the preparation and processing of the powder should be provided. Pass/fail criteria for each major processing step should be given. For a cross-linked starch, a complete description of the cross-linking process should be provided.

Manufacturing should be in compliance with current good manufacturing practices. Manufacturing guidance is available in the document titled "Guidance for the Preparation of PMA Manufacturing Information" available upon request from the Division of Small Manufacturers Assistance (DSMA).

2. Device Description (21 CFR 814.20(b)(3)(ii))

The sponsor should provide a complete and detailed description of the physical and chemical properties and specifications of the absorbable dusting powder.

The physical characterization should include data such as the color, size, and distribution of the powder particles. The chemical characterization should include the chemical composition of the powder and the chemical name, molecular formula, and quantity of each constituent.

The manufacturing specifications of the physical and chemical aspects of the powder should be fully defined. The specifications for an absorbable dusting powder should include aspects such as those described in U.S.P. for corn starch-based absorbable dusting powder. In addition, the extent to which the starch is modified in the final product should be specified. For example, the specifications for the upper and lower limits for the degree of cross-linking should be provided for a starch that has been modified by chemical cross-linking.

3. Sterilization Information

The sponsor should identify the types of sterilization processes that are compatible with the absorbable dusting powder, and the appropriate cycle parameters and conditions to be used with each method should be noted. Data should be provided demonstrating that the absorbable dusting powder is unchanged following sterilization by each method and still meets the physical and chemical specifications of the powder. In addition, the sponsor should provide information on the bioburden of the powder and on the ability of the product packaging to maintain a low bioburden in the powder during storage (shelf life stability).

4. Physical and Chemical Testing

Physical and chemical testing should be conducted to confirm that the manufacturing specifications are met. This information should include the methods and results of tests conducted to ensure that the product meets the specifications for the final product. For a corn starch-based dusting powder, the product must meet the identification found in the Federal Register, May 25, 1971 and U.S.P. specifications for Absorbable Dusting Powder. (A copy of the U.S.P. specifications is attached.) In addition, certification that the powder meets U.S.P. specifications should be provided.

Methods for monitoring the extent of the modification in the powder for compliance with the specification during the manufacturing process should be described. If the parameter cannot be measured using a direct method, an alternative method and test data should be provided which correlate the specified parameter with the indirect test method.

H. Nonclinical Studies

All testing should be conducted using samples of the finished powder sterilized by each method specified in the labeling (i.e., steam, ethylene oxide, and radiation).

1. Toxicological Studies

To ensure the safe use of absorbable dusting powder, a toxicological evaluation of the powder additives and all residues remaining associated with the powder should be submitted. This information will assist FDA in evaluating the potential health risks to patients and users that are presented by the presence of the residues.

Residues of all of the agents added to the powder during the manufacturing process should be considered. The residues that are of concern should be identified and justification should be provided for excluding any residues. Evidence then should be provided showing that the amount of each residue of concern remaining associated with the powder is at a safe level. The evaluation may be accomplished on the toxicity of the powder additives and/or any remaining toxic residues by reviewing the available information from the following sources:

a. animal toxicity studies sponsored by the manufacturers of the cross-linking agents and additives; and

b. animal toxicity studies in the published scientific literature.

Copies of all references should be provided.

If inadequate information is available from the manufacturers or the published literature, then toxicity testing for the absorbable dusting powder itself should be conducted. Because the dusting powder is considered a skin contact device, the appropriate toxicological tests for absorbable dusting powder should include:

a. Skin irritation tests
b. Skin sensitization assay

Other tests may also be deemed necessary. The applicant should refer to the ISO 10993, Part 1, "Biological Evaluation of Medical Devices"[1] for further details on biocompatibility testing of medical devices. For conducting these tests, published guidelines and methods should be referenced and a complete description of the test methods should be provided.

2. Bioabsorbability Studies

The sponsor should establish that any modification, such as cross-linking, made to the natural starch does not significantly alter the biodegradability of the starch. The need for bioabsorbability data may be addressed with in vitro testing of the modified powder for susceptibility to the digestive enzyme, amylase. The rate of enzymatic degradation of the modified starch powder, unmodified starch, and talc as a negative control (resistant to degradation) by amylase should be compared. If the difference in the rate of degradation between the modified and unmodified starch is insignificant, then we may assume that the biodegradability of the modified powder produced by the new process is comparable to that of unmodified starch. Such a result would suggest that the risk of formation of granulomas or a foreign body reaction is no greater for the modified starch than for the unmodified starch.

If the above described biodegradability data are **inadequate** to resolve concerns about the safety of the powder, then in vivo animal bioabsorbability testing should be conducted.

The applicant should refer to published literature for information about the appropriate test methods. A complete description of the in vitro and/or in vivo test methods should be provided. The applicant may provide a test protocol to the FDA for review prior to initiation of the tests. Although review of the protocol provides the applicant with comments and suggestions regarding the test method, it does not ensure that the final test protocol will be adequate.

I. Clinical Studies

It is not expected that clinical studies will be necessary to support the safety and effectiveness of absorbable dusting powder in a PMA.

J. Labeling (21 CFR 814.20(b)(10))

The methods of sterilization that are compatible with the absorbable dusting powder and the cycle parameters and conditions for each method should be stated.

K. Environmental Assessment (21 CFR 814.20(b)(11))

The sponsor may claim a categorical exclusion from the requirement of an environmental assessment but must provide information to justify the exclusion.

L. References

Use of International Standard ISO-10993, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices" (G95-1).
http://www.fda.gov/cdrh/g951.html

M. Contacts and Addresses

Further information concerning the PMA regulations and/or PMA requirements can be obtained at: http://www.fda.gov/cdrh/pmapage.html

General questions regarding the submission of premarket approval applications or requests for guidance documents should be directed to the Division of Small Manufacturers Assistance (DSMA), HFZ-220, CDRH, FDA, 1350 Piccard Drive, Rockville, Maryland 20850; phone (800) 638-2041 and FAX (301) 443-8818.

Specific questions regarding Premarket Approval Applications for medical glove dusting powders should be directed to the following address.

Chief, Infection Control Devices Branch (HFZ-420)
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Dental, Infection Control and General Hospital Devices (DDIGD)
9200 Corporate Blvd.
Rockville, MD 20850

Phone: (301) 443-8913
FAX: (301) 480-3002

ABSORBABLE DUSTING POWDER, USP

Absorbable Dusting Powder is a specially processed cornstarch. It is a substance recognized in the United States Pharmacopeia - National Formulary (USP-NF). The USP-NF is a standards setting body in the United States. The USP-NF is officially recognized in the Federal Food, Drug and Cosmetic Act (Act).

Under section 502(g) of the Act, if a product is claimed to be the same as one named in an official compendium, including the USP-NF, it must be packaged and labeled in accordance with the requirements stated in the compendium. Failure to meet this requirement causes the product to be misbranded.

Therefore, if you choose to use Absorbable Dusting Powder, USP as a donning powder or glove lubricant, the powder you use must meet the requirements stated in the current revision of the USP-NF. You can get information about obtaining a copy of the current monograph for Absorbable Dusting Powder, USP from the USP Internet web site at: http://www.usp.org/

STERILIZATION OF POWDERED GLOVES:

In addition, validation data, such as the Sterility Assurance Level (SAL) and the organism used as a biological indicator, should be provided, and the validation method for each sterilization process should be described. Since powder is sold nonsterile and is sterilized with gloves by glove manufacturer, then it is the responsibility of the glove manufacturer to validate the sterilization method.

Since surgical gloves may be labeled for resterilization if the package integrity is breached, data on the number of sterilization cycles that the powder can withstand and still remain within specifications should be provided. This is not needed since gloves should be discarded and not resterilized if the package integrity is compromised.

If sterilization with ethylene oxide is specified, then the maximum levels of residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol which may remain associated with the powder should be provided. The levels should be consistent with the draft Federal Register Notice on ethylene oxide limits. This is not needed since this is the responsibility of the glove manufacturer with the final product.

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DEFINITION AND STATUTORY AND REGULATORY REQUIREMENTS

Under the proposed rule, patient examination gloves would be Class II (special controls) devices and would be identified as follows:

Patient Examination Gloves, powdered (proposed §880.6250). A powdered patient examination glove is a disposable device made of natural rubber latex or synthetic material that bears powder to facilitate donning and is intended to be worn on the hand or finger(s) for

To keep bioburden levels low on gloves:

- the packaging, donning powder, and gloves should be kept clean throughout storage;
- all manufacturing, handling, and packaging operations should be appropriately controlled;
- spilled coagulant solution and starch slurry or former release agents should be scrupulously cleaned from the floor;
- if post-cure washing is performed, the water or gloves should be monitored and appropriately treated to control microorganisms;
- the starch slurry or other lubricant solution should be cooled, treated with a bactericide, or otherwise controlled to reduce the growth of organisms;
- any air used to cool post-cured gloves should be filtered or otherwise controlled;
- the moisture content of finished gloves should be at or below the manufacturers moisture or dryness specifications; and
- the packaged gloves should be protected from moisture and contamination during storage and shipment.

It is obvious that moist, contaminated gloves cannot meet a significant expiration period or shelf life. Maintaining a long expiration period may require establishing a specification for moisture and bioburden; controlling bioburden; monitoring the moisture content of finished gloves; and ensuring that dispenser boxes be shrink-wrapped with plastic or otherwise be protected from moisture, and other contaminants. Changes in packaging and sealing should be evaluated, validated, and, in general, meet the change control requirements of the QS regulation.

Manufacturers that want to perform tests for bioburden may refer to Association for Advancement of Medical Instrumentation (AAMI) guidelines (USA FAX 703-276-0793) or to IES-RP-CC-005-87-T for *Cleanroom Gloves and Finger Cots* or consult a microbiological test laboratory.

Sterile Examination Gloves

Gloves intended to be sterilized should be controlled as noted above in order to keep their bioburden level well below the level that can be killed by the intended sterilization process.

Information on sterilization is located in Chapter 10 under *Sterilization Notes.* Finished sterile examination gloves should meet the ASTM standards for examination gloves, ASTM D 3578, D 3772, D 5250 or an equivalent standard, as appropriate. The manufacturer should have data demonstrating that the **finished sterile** examination gloves meet all specifications,

To keep bioburden levels low on gloves:

- the packaging, donning powder, and gloves should be kept clean throughout storage;
- all manufacturing, handling, and packaging operations should be performed in an appropriately controlled environment;
- if post-cure washing is performed, the water should be monitored and appropriately treated to control microorganisms;
- spilled coagulant solution, starch slurry or former release agents should be scrupulously cleaned from the floor and equipment;
- the starch slurry or other lubricant solution should be cooled, treated with a bactericide, or otherwise controlled to reduce growth of organisms;
- any air used to cool post-cured gloves should be filtered or otherwise controlled;
- the moisture content of finished gloves should be at or below the company moisture or dryness specifications; and
- the packaged gloves should be protected from moisture and contamination during storage and shipment.

Finished sterile gloves should meet the ASTM standard for surgeon's gloves, ASTM D 3577 or an equivalent standard, as appropriate. The manufacturer should have data demonstrating that the finished sterile surgeon's gloves pass their elongation, tensile and barrier, integrity, leak or pinhole test and acceptance criteria as required by 21 CFR §820.181. (FDA uses a 1000 milliliter water leak test in accordance with the sample plan and test method in 21 CFR §800.20. On a design qualifying basis to show that they will meet the intended use or user/patient needs, the sterilized gloves should meet the manufacturers acceptance criteria for all parameters including barrier integrity after undergoing real time aging for a suitable period or suitable accelerated aging such as for 7 days at 70 degrees Centigrade as described in ASTM D 3577, or an equivalent standard. (The accelerated aging conditions are expected to change when ongoing studies are completed.) (Routine leak testing during production should be done on non-aged gloves.)

PREMARKET NOTIFICATION [510(k)] SUBMISSION FORMAT

A suggested format for the submission of a premarket notification [510(k)] for surgeon's gloves is presented on the next several pages. It is not a required format; however, it may be used as a guide for submitting the required information to FDA. This format should increase the completeness and accuracy of your submission and reduce the time required to clear your gloves for marketing.

Each 510(k) submission must be for only one type of glove such as a powder-free latex surgeon's glove. Do not mix data for multiple types of surgeon's gloves in one 510(k) submission. A

Current investigations and conventional manufacturing techniques indicate that one way of minimizing such reactions is to remove as much of the water-soluble proteins and adverse manufacturing chemicals as is feasible from latex gloves. This removal is primarily done by:

- removing or denaturing the proteins in the raw latex,
- using and controlling pre-cure leaching and post-cure washing processes,
- assuring that the leaching tanks and spray or washing tanks use water that is flow-controlled and continually refreshed to avoid chemical (manufacturing material) and protein saturation, and
- leaching and washing for an appropriate time.

Washing after curing is important because proteins become more water-soluble and/or move to the surface of latex gloves during heat curing. Thus, washing should be done before the final donning powder or lubricant, if any, is applied. Otherwise, the starch slurry tank is saturated with water-soluble proteins. Chemical residues, protein on the surface of the gloves, and protein in the slurry tank become attached to, or coat, the starch and other particulates. Later, some of the particulates with residues and protein could become airborne during handling and use of the gloves.

The temperature of the leaching and washing water should be established by each manufacturer as the temperature needed varies based on the parameters of the overall compounding, dipping and curing methods. Preliminary studies by the Malaysian Rubber Research Institute and others indicate that the purity (flow rate) and agitation of the leach water and total leaching time are more important than water temperature.

Surface treatment of the cured latex glove with chlorine or similar agents denatures surface constituents such as water-soluble proteins. These treatment processes also wash and rinse away proteins and manufacturing residues. Chlorine is an adverse manufacturing material and must be removed per §820.70(h) from the gloves after chlorination by washing, neutralization, etc

Synthetic polymer gloves, polymer-coated latex gloves, or any gloves with a labeled or controlled protein level should not be dipped in any tank (particularly starch slurry tanks) or tumbled in dryers where regular protein coated latex gloves have been produced unless the tanks are cleaned before the production of the low- or non-protein gloves. Otherwise, such low- or non-protein containing gloves may become contaminated with protein.

The processes used to control water-soluble proteins and manufacturing materials must be developed per §820.30, validated per §820.75, documented per §820.181, thereafter controlled per §§820.70 and 820.75 and operated by trained personnel. Validation guidance is available on the web at www.fda.gov/cdrh/comp/ghtfproc.html.

A suitable method should be used for sample testing for water-soluble proteins and adverse chemical residues or specific allergens during routine production. Such methods should be validated versus standard laboratory methods. Data from validation of the testing methods for proteins and manufacturing materials or specific allergens should assure that the test methods are adequate. Use of these test methods in production should show that leaching, cleaning or treating processes being used adequately reduce water-soluble proteins, adverse manufacturing materials or specific allergens to, or below, the level set in the manufacturer's specifications. (ASTM or

other standards organization may establish protein, chemical, total extractables, and/or specific allergen levels in the future. Meanwhile, manufacturers should set their own levels which should be consistent with current practice and medical needs. Please see the FDA proposed recommendations for protein and powder in Chapter 6, *Labeling*.)

Bioburden Control. Medical gloves, particularly those powdered with starch, can support the growth of micro-organisms. Therefore, processing controls, as appropriate, should include:

- purchasing starch with a low bioburden,
- properly storing the starch until it is used,
- applying starch per established procedures,
- cooling the starch slurry and/or using an antimicrobial in the starch slurry tanks,
- sampling finished gloves to assure that excessive starch is not applied,
- keeping the finished gloves clean,
- establishing and meeting a dryness specification for finished gloves, and
- protecting finished gloves from the environment.

An example which stresses the need to exercise controls over conditions related to microbial growth is demonstrated by a recall of examination gloves. It was the manufacturer's practice to reduce the temperature of the glove drying oven when serious mechanical problems occurred. After experiencing a problem and restarting the operation, a lot of insufficiently dried gloves containing cornstarch was packaged in a moist state. After distribution, a hospital called FDA and complained that they had noted a visible black film on the surface of the lot of gloves, and that their analysis revealed cultures of Aspergillus and Fusarium. Fortunately the manufacturer had lot numbers on the product which were traceable to the date the moisture problem occurred, and thus were able to restrict the recall to specific lots of examination gloves.

Finished Glove Evaluation

Finished gloves must be evaluated according to written procedures to show that the lot of meet all of the manufacturer's specifications (acceptance criteria) per §§820.80 and 820.181. The finished device evaluation must include inspection and testing of samples of completely finished gloves. Because of different flow/bleeding/leaking characteristics from pinholes, leak test procedures for synthetic polymer gloves may have to be different than for natural rubber latex. The gloves selected for testing, as appropriate, are powdered, powder-free, cured, post-washed, chlorinated, lubricated, packaged, sterilized, etc., such that they are the same as the gloves delivered to the user. Glove evaluation, as appropriate, covers parameters such as:

- width;
- length;
- weight;
- thickness;
- pin holes;
- elongation;
- cuffs/beads
- rips or tears;
- tensile strength;

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s	t	u	v	w	x
COMPONENTS, PARAMETERS AND PROCESSES	Irritation	Type IV Allergy	Type I Allergy	Barrier	Shelf Life		Tack / Grip	Bricking	Blocking	Particles	Discoloration 1/	Extractables	Donning Ease	Comfort	Roll Down	Hand Fatigue	Thickness	Uniformity	Bioburden	Endotoxins	Spoilage	Modulus		
13. POWDERED GLOVE SLURRY antimicrobial; ~~Surfactants; Ingredients;~~ Temperature; Amount used; Agitation; Microbial growth; Clean out frequency 3	✓	✓	✓					✓	✓		✓								✓	✓	✓			
14. CHLORINATION POWDER FREE GLOVES Concentration; Filtration; Duration; Load; Reversals; pH; Agitation; Drain efficacy and speed; Neutralization; Rinse Quality	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓		✓		
15. LUBRICANT Type; Concentration; Distribution; Microbial Growth	✓	✓					✓	✓	✓				✓						✓	✓	✓			
16. DRYERS Delay; Temperature; Duration; Cross Contamination; Humidity; Filtration; Load / Space; Airflow	✓			✓	✓			✓	✓	✓	✓	✓							✓	✓	✓	✓		
17. PACKAGING Line Clear; Clean up; Label control; Packaging material; Stack method; Sun / light exposure 4, 5			✓	✓	✓					✓	✓	✓							✓	✓	✓			
18. TRANSPORT / STORAGE Temperature; Moisture; Protection; Insulation	✓			✓	✓			✓	✓	✓	✓	✓							✓	✓	✓			
19. CLEANING HOW? WHEN? Formers; Filters / Screens; Tanks; Mop (no sweeping); Air / Surface; Line Change; Personnel; Chain guards	✓	✓	✓	✓	✓					✓		✓							✓	✓	✓			
20. COATINGS Laminates, Bound polymers 6	✓	✓					✓			✓		✓	✓	✓		✓	✓	✓				✓		
21. EXTRACT TREATMENTS Enzymes, Protein binders	✓	✓	✓	✓	✓					✓		✓												
22. Other (Add for your glove and processes)																								

GENERAL: Line speed alters the dynamics of every step and process. Environmental conditions impact barrier, quality, appearance, etc. Parameters in general are interdependent. Standing water or wet glove on hold is a potential problem: microbial endotoxin, oxidation. Sterilization must be closely monitored with routine checks on glove and packaging bioburden.

Notes: 1. Also affects drying inside the bead 2. Can cause gloves to be brittle 3. Slurry also affects powder distribution
4. Sidedness 5. Mixes 6. Delamination potential

1/ Refers to yellow in latex affected by carotenes 2/ Rolldown of hand or glove material.

EXHIBIT B

Citizen's Petition to the Food and Drug Administration to Ban Cornstarch Powder on Medical Gloves

February 24, 2009

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Commissioner
Food and Drug Administration
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Rockville, MD 20857

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Director
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
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Mail code HFA-305
301-827-6860

CITIZEN PETITION

The undersigned submits this petition under be appropriate action as defined in **Sec. 516** [21 USC 360f] **Banned Devices**, of the Federal Food, Drug, and Cosmetic Act, or any other statutory provision for which authority has been granted to the Commissioner of Food and Drugs (under 21 CFR, Part 5.10) to request the Commissioner of Food and Drugs to ban cornstarch powder on medical gloves.

We hereby petition the Food and Drug Administration (FDA) to ban the use of cross-linked cornstarch powder (so called "Absorbable Dusting Powder") on surgical and examination gloves. Powder presents serious potential consequences for patients and healthcare providers. This applies to all medical gloves whether made of natural rubber latex or synthetic materials for reasons that will be highlighted in this petition. We support the FDA petition to ban powder dated September 1, 2008 by Dr Richard Edlich, et al, and intend this petition as additional substantiation of those efforts.

Banning powder is not a new concept. Many individual hospitals and Integrated Health Networks have done so as have countries including Germany (1997) and the National Health Services of the United Kingdom who ceased to purchase powdered examination and surgical gloves in 2000. Several hospitals

in the US have successfully banned powdered gloves. A survey conducted by Jackson identified 70 hospitals in the United States using only powder-free gloves.[1] Under the direction of Dr. William B. Long III, Director of Trauma Specialists LLP., Legacy Emanuel Hospital, in Portland OR, the Legacy Healthcare System in Washington and Oregon banned powdered gloves in 2001.

An extensive survey by GHX Market Intelligence in Louisville, CO. (USA) of the second quarter 2008 market research data of gloves used in the United States, showed the following for total examination glove market (physician offices, surgery centers, and hospitals): Powder-free examination gloves (units) 94.4%; powdered exam gloves (units) 5.6%; and for the surgical glove market: Powder-free surgical gloves (units) 64.6%; powdered surgical gloves (units) 35.4%. With all the data emphasizing post-surgical complications caused by powder in the surgical wound, it is inconceivable that over 30% of surgical gloves are still powdered.

Even the 5.6% powdered examination glove level is unacceptable. In some facilities, powdered examination gloves may only make up 1% to 2% of their examination glove purchase, but the powder does not "just" stay in the realm of the powdered glove being worn while performing a particular task or procedure. Powder is readily aerosolized and settles on surfaces throughout the hospital. It is almost impossible to have truly "powder-free zones" in a hospital environment that has any powdered gloves. Glove powder is dispersed onto gowns, lab coats, masks, floors, walls, above ceiling tiles, through non-HEPA air handling systems, on instruments during cleaning, assembly, or while in the open environment, on contact surfaces in isolation rooms, open boxes of supplies, computer key boards, records, upholstery, nursing stations, carpets, on sterile packs being transported to ORs, on monitors, into corners , behind equipment and into the OR by various means (sterile and unsterile) including exam gloves worn by the CRNAs, anesthesiologist, circulators, cleaning crew or Central Services.

The only to stop powder contamination from gloves is to ban them.

History

Talcum powder (hydrous magnesium silicate) and Lycopodium spores (club moss) were originally used to facilitate glove donning and prevent gloves from blocking or sticking together in the package. In the 1930's, Lycopodium was found to cause severe granulomas and adhesions, identified as toxic and its use stopped. In the early 1940's, talc was found to cause similar post-surgical complications. In 1947, Lee published studies recommending the use of cross-linked cornstarch as an alternative glove powder.[2] However, by 1952, Lee published doubts as to the safety of this cross-linked cornstarch[3] after repeatedly observing acute and severe inflammation, dispersed granulomas and adhesion formation after both experimental and clinical procedures. At that time, there were no powder-free gloves and no "safe powder" alternatives, so the Food and Drug Administration (FDA) required a powder cautionary statement to be placed on all surgical glove packaging in 1971:

> "Caution: After donning, remove powder by wiping gloves thoroughly with a sterile wet sponge, sterile wet towel, or other effective method"

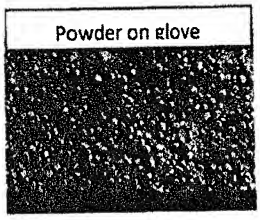
Efforts by manufacturers, suppliers, clinicians, test laboratories and the FDA through organization of the American Society of Testing and Materials (ASTM), worked diligently to develop a standardized test method for measuring the amount of powder on a glove – ASTM D6124. Alternative methods of glove lubricity have been developed by manufacturers to compensate for the lower powder levels. Powder-free gloves were also developed and improved upon increasing their manufacturability and user-appeal significantly. Several manufacturers and researchers published methods for reducing powder as they were developed so all could benefit and speed efforts at overall powder reduction. Powder levels on latex and synthetic, examination and surgical gloves decreased significantly. Simultaneously, test methods and protein reduction requirements for natural rubber latex (NRL) gloves were established and pushed forward by ASTM committee participants. Protein and Powder reduction were a tremendously successful joint effort. FDA added requirements in submissions and inspections adding teeth, beyond the aggressive, but voluntary ASTM powder and protein standards activities. We were successful – but this is only reduction, not abstinence.

However, the **FDA has recently removed the previously required powder caution statement** for the following reasons:

1) Powder levels have now been reduced
2) Latex allergy prevalence is decreased and new cases are extremely rare
3) Fears that attempts to wipe powder off gloves actually lead to powder aggregates or clumps, increasing the probability and or the severity of adverse biological consequences

Left as is, the implication is that glove powder is safe if it is not clumped. Not true. The primary person at risk here is the patient. In this time of supposed full disclosure, patients are not aware of the added risks they are subjected to unnecessarily.

"True" characterization of glove powder



Glove powder is made of cornstarch cross-linked with epichlorhydrin or phosphorus oxychloride. Cross-linking prevents the powder from dissolving during steam sterilization (the method by which gloves were formerly sterilized) or turning into paste on sweaty hands during use. The powder is required to withstand boiling for 20 minutes and continue suspended for an additional 24 hours without dissolving. This rigorous test remains a requirement for being labeled official "Absorbable Dusting Powder" (ADP) as described in the United States Pharmacopeia[4] highlighting how difficult it is to dissolve cross-linked cornstarch glove powder. The use of ADP qualified glove powder is a requirement for powdered surgical gloves and is used almost exclusively for powdered examination gloves.

The ADP powder is purchased by glove manufacturers and added to a water slurry suspension containing additives and preservatives. The unfinished glove is dipped into the powder slurry where it "picks up" the powder.

ADP glove powder as it arrives to the manufacturer, before it has been placed on the glove, has been shown repeatedly to cause acute severe inflammation, granulomas and adhesions as noted in studies conducted with ADP cornstarch powder suspended in physiological saline. However, the powder that ends up inside the patient post-surgically is not the same pristine powder, but is instead contaminated by many different substances. It is currently widely understood that powder particles absorb protein, and that protein can remain attached to, and transported by powder particles.[5] However, it is not widely known that the glove powder particles that end up in patients are much more bio-active also containing the chemicals, endotoxin, and other substances absorbed during the manufacturing process.[6,7]

Powder contaminants: Chemicals and proteins encountered glove manufacture[8,9]

- Chemicals and proteins encountered during the manufacture of natural rubber latex (NRL) gloves include different combinations of cross-linking agents including sulfur with accelerators such as carbamates, thiurams, thiazoles, thioureas, guanidines, xanthates or sulfenamides; accelerator activators including metal oxides, organic acids or amines; amines and ammonia for pH control (maintains high pH to speed cure rate); antioxidants, antiozonants and stabilizers such as substituted phenylenediamines, phenolics or phosphate compounds together with protective stearates and waxes; fillers such as clay and calcium carbonate; pigments such as titanium dioxide. Powder absorbs these chemicals. Proteins from the rubber tree, *Hevea brasiliensis*, have also been shown to be absorbed and transported on powder and as such are capable of eliciting a reaction in sensitized individuals.
- Nitrile gloves utilize just about all the same chemical constituents, except that there is no natural rubber latex. Instead, acrylonitrile and butadiene added at different proportions are cross-linked to provide elasticity. Additional pigments are often utilized.
- Vinyl gloves are composed of quite different ingredients including plasticizers such as phthalate esters (Di-2-ethylhexyl phthalate: DEHP; also called di-octyl phthalate or DOP), diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP), thermal stabilizers, lubricants, pigments, flow modifiers, UV stabilizers, and fillers-however, these chemicals can similarly be absorbed by powder particles.
- There are other base glove materials such as polyisoprene, styrene-butadiene, neoprene and polyurethane. Each category incorporates its own set of compounding chemicals. Because they currently represent a very small portion of the market, we will not go into detail on their chemical composition.

Many of these absorbed substances are:

- Irritants that initiate or augment existing inflammatory response levels
- Type IV chemical sensitizers that can elicit delayed type hypersensitivity reactions and even result in implant, transplant or graft rejection
- Type I allergens such as natural rubber latex (NRL)proteins
- Pyrogenic endotoxins with numerous bio-active pathways

Powder contaminants: Endotoxins

With the exception of vinyl gloves, cornstarch powder is almost exclusively applied by dipping the gloves into a powder-slurry containing water, dispersion facilitators, pH adjusters, preservatives and the cross-linked cornstarch powder. The slurry is made warm by the constant introduction of the hot gloved formers. The warm water and cornstarch powder food source provide an excellent environment for microbial growth and reproduction. As the slurry is often in place for days to weeks at a time and only "topped-off" as volume is needed, microbial populations can readily exceed 10^9/mL. Endotoxin (lipopolysaccharides from the bacterial cell wall of gram negative bacteria) levels can be extremely high. Surgical gloves are, of course, sterile. However, endotoxin is not destroyed by glove sterilization methods which include ethylene oxide sterilization, steam, gamma or E-beam sterilization, and so remains biologically active even on sterile surgical gloves. No endotoxin limits have been placed on gloves even though surgical gloves frequently handle devices required to be non-pyrogenic (very low endotoxin) rendering these devices pyrogenic.[10,11,12,13]

Powder plus contaminants as a unit into the patient: The chemicals, allergens and endotoxin summarized above will, in numerous combinations and quantities, are absorbed into, and adsorbed onto, the glove powder particles. Although the heaviest concentration of powder is on the inner surface of the glove utilized as a donning agent, tumble-drying, sorting and packaging operations ensure that powder is also on the exterior of the glove. Coupled with the powder that escapes gloves when torn or perforated in use, the probability of powder contaminating the surgical site, trauma wounds, burn injuries, diabetic ulcers, etc., when powdered gloves are worn certainly approaches 100 percent. The amount that enters the patient receives depends on how much powder is on the glove, how many hands enter the site, the gloves that handled the devices entering body tissues, the number of tears and perforations that occur and the amount of powder aerosolized by any of the surgical or exam gloves in the area.

Powder contamination during clinical use: There is another source of contamination often neglected in considerations of powder safety – contamination of the powder while in clinical use. Disinfectants, patient bodily fluids, infectious microorganisms,[14] drugs or antibiotics and other substances with which the glove comes in contact add to the powder contamination profile.

The National Institute for Occupational Safety and Health (NIOSH) alert states: "Warning! Working with or near hazardous drugs in healthcare settings may cause skin rashes, infertility, miscarriage, birth defects, and possible leukemia and other cancers."[15] Recognizing that cytotoxic chemo-drugs can be absorbed and transported by powder posing risks to personnel, the Oncology Nursing Society in their Chemotherapy & Biohazard Guidelines Recommendations for Practice states that gloves must be powder-free. However, this does not address powder entering from powdered gloves used for other the tasks in the area.

A significant percentage of staff at Brigham and Woman's Hospital in Boston experienced numerous respiratory and other health problem complaints in 1993. Efforts to rid the facility of powder, its contaminants and other environmental accumulations above ceiling tiles, in furniture, in drapes, around equipment, on top of cabinets, in carpets, etc., cost millions of dollars. The facility converted to powder-

free examination gloves and has become increasingly powder-free in the OR. The clean-up and subsequent conversion to "almost" powder-free dramatically reduced staff occupational health complaints.

Aerosolization and fall out of these powders contaminated in use is a threat to patients, health care providers and other individuals in the area.

Longevity: The length of time glove starch powder may persist in the body varies drastically from as little as 24 hours in studies using pristine ADP (from the bag without undergoing exposure to glove manufacturing chemicals or the clinical experience) to over 4 years (identified enclosed in granulomatous nodules encased in adhesions).[16,17,18] Consequences of powder may start immediately or be delayed for years as the biological response matures. The consequences may far out-last the presence of powder as it may finally be dissolved, but leave adhesions or other complications in place.

Pathology

Pathological activity overview: Glove powder-associated mechanisms of induced pathology may be of acute or delayed onset; of short term or prolonged duration; and with limited or severe consequences. Biological responses will, of course, depend on the amount and type of chemicals on the powder; whether or not the patient or wearer is genetically prone to be sensitized and has or has not been sensitized; whether or not consequential combinations of substances are present (ex. Type IV or Type I sensitizers and endotoxin); amount of trauma sustained, patient's nutritional status, etc. Glove powder particles with their absorbed and adsorbed chemicals, endotoxins and substances acquired from the glove manufacturing process and in–use contaminates can cause or exacerbate:

- Increased risk of infection
- Irritation – physical abrasion and chemical irritation
- Inflammation – acute or chronic
- Pyrogenic activity including local or systemic responses (ex. fevers of unknown origin). If enough endotoxin is present, it can precipitate local or systemic complement cascade activity, activate macrophages, and initiate release of a plethora of cytokines, etc.
- Type IV hypersensitivity (delayed type hypersensitivity or cell-mediated response)
- Type I hypersensitivity (immediate type hypersensitivity; anaphylactic response; IgE mediated response)
- Anaphylactoid responses
- Respiratory complications (Type I or Type IV response activation; irritant or endotoxin induced pulmonary aggravation)
- Adjuvant activity for exposure to other, non-glove associated allergens or chemical sensitizers

Symptoms may be delayed due to type of pathological mechanism. For example an initial acute inflammatory response may occur and symptoms present within hours to days and affect a number of patients; while a Type IV, delayed type hypersensitivity component may take 48-72 hours for an initial response, followed by weeks to months for adhesiogenesis and tissue maturation and affect a limited

number of individuals. Symptoms may also be delayed or prolonged because biological activities to wall-off the powder particle as a foreign body creating granulomas and adhesions actually setting the encased powder particles up as hubs or individual foci of activity as the chemicals slowly leach out through their encasing biological structures within the patient. The individual carrying around "slow-releasers" may reach a threshold level of conversion from the sensitization phase to being a sensitized individual. Subsequent exposure to the sensitizer either via leaching from same adhesion-encased slow-release powder particles, or from subsequent surgeries, results in symptom expression.

Because only genetically predisposed individuals have the capacity to become sensitized to a specific chemical, these more-serious Type IV reactions do not occur in the majority of patients. This goes a long way toward understanding why say 20 patients undergoing the same procedure have no reportable problems save perhaps some pain or inflammation that rapidly subsides. Perhaps the 21st patient will be the individual with the Type IV reaction presenting with severe adhesions requiring resurgery for bowel obstruction three years after the original surgery.

It is important to note, that histopathological investigations as to the initiation of granulomas and adhesion tissues may be left without finding the initiating agent as it may have finally been degraded and absorbed. However, resulting granuloma nodules, adhesions, constriction bands or the state of being sensitized (Type I or Type IV), may persist for weeks, months, years or a life-time.

What does this mean to the patient? What are the complications associated with glove powder?

Increased risk of infection: Within a very short time of glove powder deposition, a localized acute inflammatory response is initiated. This triggering of the immune cells depletes the protective area's local capacity to protect against microbial threats. The defense response is instead directed toward the much larger and more reactive threat posed by the powder particles and their adherent chemicals, endotoxins and possible proteins. For example, a few microorganisms usually contaminate the surgical wound. These organisms are normally killed and removed before they have a chance to become an infection. However, the "distraction" powder is capable of producing can give bacteria just the time needed to multiply and gain a foothold. After they have released a number of pro-inflammatory chemokines, local macrophages die proportionate with the amount of powder deposited further depleting the available general defense ammunition.

- Jaffray confirmed this reduced resistance to infection by exposing clean wounds to equal challenges of *Staphylococcus aureus*. Into one group of animals, he also added 2 mg of sterile ADP cornstarch powder. The infection rate increased from 1 in 9 animals acquiring and infection (without powder) to 9 out of 10 animals where powder had been co-introduced.[19]
- Ruhl, using 5, 10 and 15 mg of ADP cornstarch powder placed into wounds (10 animals for each powder level) containing equal challenges of *Staphylococcus aureus* demonstrated a dose response relationship between the amount of powder used and the number of bacteria recovered after 4 days of occluded incubation. The greater the amount of powder, the greater the number of Staphylococcus that survived and thrived in the distracted environment. All three doses yielded a significantly higher titer of bacteria than controls with no powder.[20]

- Odum, using a model similar to that of Ruhl, confirmed that ADP cornstarch powder significantly potentiates bacterial growth and enhances a wound's inflammatory response assessed by measuring induration of the wound's edges.[21]

If powder particles are clumped, bacteria can find protection from white cell attacks either within the powder-aggregate structure, within the granuloma potentially formed or on an implant sheltered under adherent powder particles. In such protected shelters, the bacteria can attach, multiply and exude a protective matrix initiating biofilm formation within hours. Here they can increase in numbers without displaying overt signs of infection. Recognition may not occur for days, weeks or months after long term symptoms difficult to diagnose.

Powder carries bacteria. Powder can also carry bacteria as demonstrated in studies by Newsome and Shaw.[22] Cultured air filters showed starch particles at the center of many bacterial colonies. Subsequent air sampling throughout the same hospital (intensive care, surgery, scrub rooms, and laboratories) revealed a significant increase of bacteria in areas where powdered gloves were worn over their areas that used powder-free gloves. Edmiston identified the same phenomenon in the OR.[23]

Wound healing complications: The presence of glove powder in a wound delays healing while it prolongs inflammation and produces repair tissue that has increased scarring, but decreased strength, elasticity and toughness.[24,25,26] This can potentially result in incisional scar dehiscence, unacceptable aesthetic appearance, lingering pain or dysfunction.[27,28] Histopathology studies performed on abdominal incisional scars where powder contamination was present, observed the same T-cell profile orchestrating the same sequence of cell recruitment and cytokine production observed in granuloma and adhesion generation confirming the powder induced immunological response. This carries through with three significant pathologies: granuloma formation, adhesiogenesis, and poor quality wound healing.

Granulomas: Powder particles form granulomas by two different primary pathways.

1. Foreign body granulomas-often referred to as the non-immunological pathway: Foreign body granulomas form as a response to the physical presence of a rather inert particle. The particle causes a physical irritation and may also have a bio-reactive profile of chemical irritants amplifying the irritant inflammatory response. Zimmerli,[29] and more recently Renz,[30] demonstrated that when polymorphonuclear leukocytes (PMNs) come into contact with foreign debris that is too large to be phagocytized, they expel myeloperoxidaze in the direction of the micro-bodies (particles), attempting to kill the perceived threat. This leaves the local PMNs with depleted phagocytic capabilities, reduced granule content, and diminished capacity to mount a respiratory burst. As PMNs are the first line of defense, the burden of protection is then shifted to the macrophage. Local macrophages are attracted to the particle that the PMNs have been incapable of removing. Initially they will attempt to phagocytize and destroy it. When unsuccessful, epitheliod cells can be identified in the fray with more macrophages arriving. Many of the macrophages or epitheliod cells will merge into multinucleated giant cells in an effort to engulf the proportionately large invader to wall it off, attempting to prevent it from posing a threat to the rest of the body. As frustrated attempts continue, chemokines are released from desperate macrophages heralding a mounting inflammatory response, signaling lymphocytes, neutrophils, eosinophils, fibroblasts and collagen to join the growing matrix

around the particle(s). Strict foreign body granulomas may be distinguished from their immunological alternatives by their relative absence of T-cells and the positioning of nuclei around the periphery of their giant cells rather than dispersed throughout the cytoplasm as seen in immunologically induced granuloma giant cells.[31] Anyone can experience a foreign body response.

2. Immunological granulomas-Type IV immunological pathway: As noted, powder absorbs chemicals from the glove manufacturing process. Many chemicals used by various manufacturers are Type IV sensitizers.[32,33] When powder particles with adherent chemical sensitizers are left in the wound of a susceptible patient, sensitization is initiated. This involves CD4+ αβ T cells with a Th1 phenotype, as well as CD8+ T cells and activated macrophages. **(This is critically important information and you will see the same cells orchestrating adhesion formation in brief below.)** After the patient has reached the threshold for symptom expression, a delayed type hypersensitivity reaction to sensitizing chemicals continually leaching from the granuloma encased powder particles or from newly introduction powder with the same chemicals during subsequent surgeries is elicited. The immunological pathway is much more reactive involving more cell types and the release of more cytokines—for those individuals capable of being sensitized. Via this mechanism, first the PMNs and local macrophages respond to the physical presence of the particle with the same depletion of their killing capability and the death of many macrophages. Then T cells rapidly swarm in taking the orchestrating role. They signal more activated macrophages in, forming an encasing matrix around the chemical eluting nidus. As the entrapped particle continues to leach out the chemical sensitizers, the delayed hypersensitivity response continues to mount. This reaction includes the recruitment of activated sensitizer-specific T cells with a greater influx of activated macrophages. Inflammation escalates precipitated by the T cell chemokine IL 17 and by cytokines from the recruited activated macrophages. Epitheliod and giant cells form in an attempt to "destroy" the reactive particle.[34] The immunological pathway of granuloma formation is distinguished by its heavy infiltration of T cells and the dispersion of nuclei throughout the cytoplasm of the associated giant cells.[35] Immunological granulomas tend to persist much longer and continue disturbing the defense system of sensitized patients in a potentially chronic manner depending on the composition of the particle's reactive-profile.[36]

Unfortunately, histological examination of excised granulomas or adhesions is not routinely performed as causation is rarely investigated. Thus neither is the identity of the initiating nidus nor the pathological mechanism usually determined.

Glove powder peritonitis: There have been numerous reports of glove starch peritonitis.[37,38,39,40,41,42,43,44,45,46,47,48,49] Symptoms normally appear 2 to 4 weeks after surgery with abdominal distension and pain being the primary complaints and low grade fever present in some cases. Severity ranges from mild to severe and life-threatening.

Numerous chemokines are released as the fray continues following granuloma formation, elevating the intensity of inflammatory response and the breadth of "territory" affected. Serous fluids fill the abdominal cavity in response to the inflammation. The swelling can be so severe that pressure is put on the heart and lungs producing rapid shallow breathing and tachycardia. The patient may have chills and a fever. The febrile response may be caused by the inflammation, triggered by endotoxins from infecting bacteria, or potentiated by endotoxins introduced as contaminants on particles. If endotoxins

are present, the complement cascade is triggered, depleting the major chemical means of non-specific defense against invading pathogens. **There may or may not be an infection, but the stage is set with a weakened, stressed immune system, creating increased vulnerability for opportunistic infection.** Inflammation is excessive, injuring healthy tissues. Hypoxia starts to become an issue impacting cellular and tissue responses as the fluids increase space between oxygen delivering blood vessels and mounting pressure reduces blood flow.

Successful treatment with corticosteroids has been reported. Because of the positive response to steroids, the frequent presence of eosinophilia, and the delayed onset of symptoms, it is thought that glove cornstarch powder peritonitis syndrome is a delayed hypersensitivity to the powder.[50,51,52] In separate experiments, Renz incubated glove powder from three commonly used gloves with monocytes from rats and humans.[53] The powder from all three gloves produced large amounts of tumor necrosis factor-alpha (TNFα), interleukin-1 (IL-1), prostaglandin E_2 thromboxane B_2, and hydrogen peroxide. Release of these mediators was associated with progressive death of the macrophages further reducing the patient's resistance to infection. Glove powder has also been reported to have cytotoxic activity against endothelial cells adding to the overall pathology.[54]

This set of activities is not only an important part of the pathology of glove starch peritonitis, but also provides a significant mechanistic explanation for much of glove powder-induced adhesion formation.

Adhesions: Post-surgical adhesions are tissues that develop uniting two damaged or reactive surfaces. Fibrin is deposited to begin the repair process usually within 3 hours of surgery.[55] The resulting delicate fibrinous adhesions are either lysed by the plasminogen-plasmin cascade or organized into permanent fibrous adhesions. In-growth of fibroblasts begin in about 5 days if the fibrin is still present.[56] The collagen derived from the fibroblast is deposited, increasing the density of the maturing adhesion. Capillaries bring in needed blood supplies while nerve fibers, muscle cells and even adipose give density to the neo-tissue.[57,58,59]

What determines whether or not the fibrin structures are absorbed or become organized is presented in the figure below.

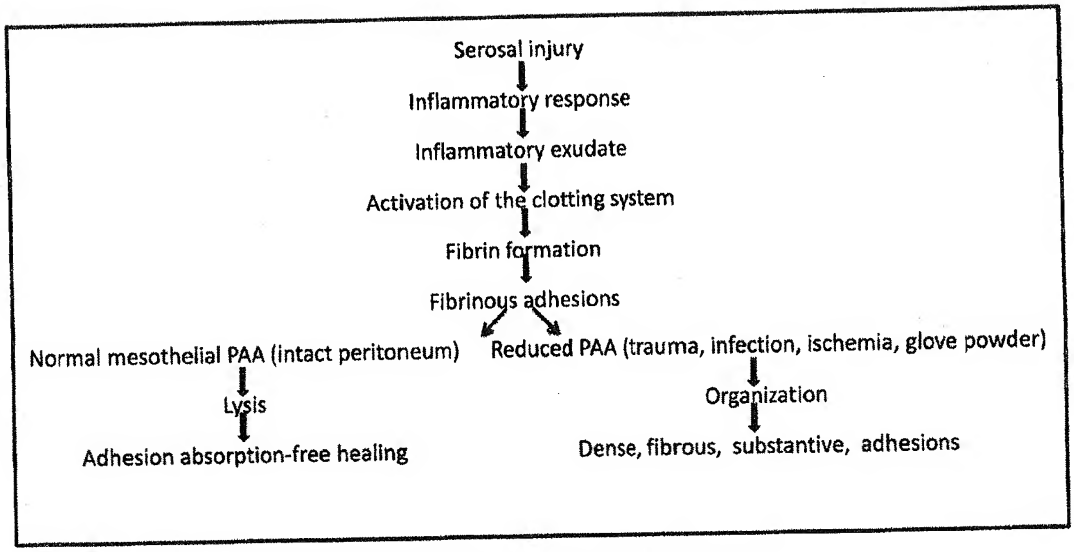


Fig. 1 Adhesion development and differentiation
Adhesions are a consequence of disturbed reparative remodeling
PAA: Plasminogen Activating Activity
Adapted from DiZerega, Gere S. 2000. *Peritoneal surgery*. New York: Springer): pg 211

More extensive, dense adhesions often contain multiple granulomas with foreign bodies at their core, suggesting a relationship between the presence of physically or chemically irritating granulomas and the development of substantive, persistent adhesions.[60] Based on the evidence demonstrating that glove starch peritonitis is an immunological reaction to powder, and that there is a well defined immunological pathway for glove starch granuloma formation, the way was opened for exploring the immunological response to glove powder in the formation of adhesions.

T-cell orchestration of adhesiogenesis-A tie into glove powder hypersensitivity the immunological pathway of granuloma formation: The mesothelium is the main defense against adhesions via its role of providing tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA)[61,62,63] the primary activators of fibrinolysis in the peritoneum.[64] The release of TNF-α, IL-1, prostaglandin E_2, thromboxane B_2, and hydrogen peroxide as demonstrated in the Renz study described earlier undoubtedly has a role in adhesiogenesis. TNF-α was found to reduce the release of tPA when added to mesothelial cells thus reducing lysis of the fibrin.[65,66,67,68,69] Simultaneously, plasminogen activator inhibitor type-1 (PAI-1) is increased in the presence of TGF-β1 (also released in the presence of glove powder). PAI also inhibits the lysis of fibrin by inhibiting plasmin production of tPA. While this prevention of fibrin lysis is occurring, transforming growth factor-β1 along with intracellular adhesion molecule-1 and vascular cell-adhesion molecule-1, downstream mediators of substance P action, associated with adhesion formation.[70,71] Thus, fibrinolysis of the early filmy fibrin is inhibited while

tissue enhancement signal is increased, setting the stage for adhesiogenesis. IL-1 is also released by the macrophages in contact with powder and has been reported to have the same effect.[72,73,74,75] The pro-inflammatory mediators IL -8, which stimulate the migration of neutrophils into the area[76,77] and the release of IL-6,[78] IL-α and IL-β[79] all have similar effects on the mesothelial cells.

Tying in the glove powder hypersensitivity with the pro-inflammatory pathway: Recent studies have shown that activated CD4+ αβ T cells with a Th1 phenotype orchestrate the events that lead to inflammatory host responses, ultimately directing adhesion composition and structure. A 2002 study by Chung at the Brigham and Women's Hospital and Harvard Medical School,[80] established that T-cells hone into the sites of surgical trauma after which they continued to increase in numbers. PMN infiltration begins about 6 hours after surgery followed by macrophage arrival at about 24 hours. T cell-derived pro-inflammatory cytokine IL-17 regulates this PMN infiltration. Chung noted that T cells were the only IL-17 producers present in the peritoneal site of surgical trauma, further validating the critical T cell role in initiating this cascade. IL-17 also elicits the CXC chemokines MIP-2 and KC from peritoneal mesothelial cells during this T-cell initiated inflammation.

This is the same pathogenesis we described for glove powder induced immunological granulomas. The same CD4+ αβ T cells with a Th1 phenotype produce the same IL 17 chemokine activating the same influx of more T cells and activated macrophages. Similarly, the fact that most studies report increasing numbers and severity of adhesions with subsequent surgeries underlines the probability of a "biological memory" component such as occurs during sensitization. This underlines the Type IV connection of powder's role in adhesiogenesis.

Endotoxin: Endotoxin has been shown to significantly reduce the fibrinolytic activity of mesothelial cells,[81,82,83] preventing fibrin breakdown and contributing to adhesiogenesis. Endotoxin from gloves can readily be transferred directly into wounds or onto devices. There, they can also function as adjuvants increasing the rate at which coincidentally introduced chemical sensitizers breach their threshold of sensitization. When endotoxin contaminated devices are placed into the circulatory system (ex. angiocatheters, heart valves, vascular grafts, central venous catheters) or in the body generally (ex. pace makers, shunts, orthopedic implants, hernia mesh), they can induce "fevers of unknown origin"; initiate and potentiate acute inflammation, activate the complement cascade and precipitate clot or thrombus formation. In higher doses, endotoxin can send a patient into shock, cause disseminated intravascular coagulation (DIC), and contribute to multi-organ failure.

Clinical Examples

Powder particles with adherent irritating and sensitizing chemicals along with endotoxins are neither the sole, nor even the major, cause of post-surgical granulomas or adhesions. But they are a significant cause and undoubtedly an amplification contributor. Most importantly, powder is a source of post treatment complications that can be stopped now! To emphasize the significance of these complications, the following studies and clinical reports are provided.

Intra-abdominal Complications: Adhesions between the wound and the omentum occur in over 88% of patients undergoing abdominal surgery and involve the intestines in approximately 50% of the patients.[84] As noted, many will be re-absorbed by the body, resulting in only minimal pain or restricted movement or function, if any. Others will continue to grow, becoming dense, vascular, and persistent. Unfortunately, some will constrict around organs causing intestinal obstruction or around the organ's blood supply causing ischemic injury and potential organ death (kidneys, intestines, gall bladder, etc.)[85] Pain, dysfunction, re-surgery, organ failure, needed transplants and even death can result.

A 1988 study reported that there were 281,982 hospitalizations for adhesiolysis (cutting away adhesions) accounting for 948,727 days of inpatient care.[86] It has been estimated that one third of all intestinal obstructions are caused by post-surgical adhesions.[87,88,89,90,91] Resurgery for adhesiolysis incurs up to 15% mortality rate.[92] One route of pathogenesis is via glove-starch peritonitis syndrome which usually appears between 1 and 4 weeks followed by a wide range of possibilities: resolution, chronic inflammatory response, granulomas nodular encasement, and/or adhesion formation.

Ellis reported that the incidence of adhesions was 88% in patients subjected to laparotomies following previous abdominal surgery.[93] This indicates the possibility of sensitization to chemicals on the surface of the powder during the initial powder deposition followed by a delayed hypersensitivity reaction (Type IV) to the chemical(s) after the powder was introduced the second time(the accelerators such as mecaptobenzylthioazol [MBT], thiurams and carbamates are potential type IV sensitizers).

It is also important to note that surgeons are often unaware that powder contaminates endoscopic surgeries as well. Although the transition into less invasive intra-abdominal surgeries does reduce the amount of powder-associated post-surgical complications due to reduced tissue trauma and reduced exposure, it does not mean avoidance of such complications. Many of our vascular and extradural catheters as well as Penrose drains, wound drains, and other devices are made of plastic, nylon or other static generating material. Static "cling" attracts the powder from the glove manipulating it as well as from anywhere nearby where the particles may have been dispersed. Endoscopes are contaminated with these particles while being inserted and manipulated by powdered gloves. Professionals performing endoscopic procedures have often made statements similar to "powder-free gloves are not necessary in laparoscopic or other endoscopic procedures as there are no open wounds for the powder to fall into", highlighting the need for an official ban rather than an educational or market pressure approach alone. Contamination of the abdominal cavity has also occurred as a result of peritoneal dialysis where assembly and delivery is often performed with sterile powdered surgical gloves. Adhesions are widely dispersed for widespread impact when associated with dialysis, as the fluid delivered flows throughout the vulnerable peritoneal cavity.[94] Due to the fluids in the abdominal cavity, migration of powder to remote regions is possible.[95]

Female reproductive complications: It has been estimated that glove powder is responsible for 15% to 20% of all female infertility[96,97] based on histological studies performed on adhesions found around reproductive organs of infertile women. Powder-associated adhesions may be found within the uterus, within or around the fallopian tubes, and associated with ovaries.[98] Consequences include physical hindrance of egg, sperm and embryo migration as well as tissue strangulation and ensuing local ischemia

resulting in longer term consequences including poor follicular development,[99] failed conception, failed embryo implantation, ectopic pregnancies, hindered embryo development and rejection.[100] Surgical lysis of these adhesions improves pregnancy rates by 38% to 52 %.[101] Percentages of successful pregnancies are lower than desired due to scars and other damage already caused by the initial adhesions as well as by new adhesions generated following the adhesiolysis surgery.

Powder can enter the female reproductive tract not only by direct implantation from contaminated gloves touching the tissues, and from powder –contaminated instruments entering the surgical field, but also from powdered examination gloves and powder-contaminated instruments introduced into the vaginal vault during gynecological examinations.[102,103,104,105] This was shown to be the case in a rabbit model in 1997 by Edelstam, Ellis and Sjösten.[106] The same team reported migration in a human clinical study in 2004, demonstrating migration from the vagina, into the cervical canal, the uterine cavity and through the Fallopian tubes up to 4 days after gynecological examination using powdered examination gloves.[107] Confirmation of this migration potential was reported by Ylikorkala in 2001, when he demonstrated that tubal ligation prevents access of the powder into the peritoneal cavity through the Fallopian tubes.[108]

Other adhesion-related complications following gynecological surgery include intestinal obstruction, chronic pelvic pain, urethral obstruction, and voiding dysfunction.[109]

Hernia and testicular complications: Hernia and testicular complications have been reported as a result of glove powder. Starch deposited during inguinal hernia repair caused complications from the operative site into the groin, requiring resurgery.[110] A dramatic example of the migration capability of powder once inside the wound is that experienced by Sugarbaker where a patient with inflammation and remarkable swelling from glove starch started at the incision site, extended into the scrotum and down the entire right lower extremity. This also demonstrates the migration potential of powder once it is in the body.[111]

Cardio-vascular complications: Powder-induced fibrosis, granulomatous endocarditis and thrombi have been reported as complications of cardiac catheterization.[112]

A study by Whelan on stent biocompatibility implanted 147 stents under full operating room conditions. The study was conducted for 12 weeks. Of the 46 animals randomly sampled, 12 experienced stent thrombosis. Histological examination of thin layered clot sections under polarized light, followed by Periodic Acid Schiff (PAS) staining, revealed cornstarch glove powder in the center of 42%. Without histological investigation there would have been no thought as to the possibility of particulate contamination as the causative agent.[113] Further tissue studies revealed particles covered in inflammatory cells in capillaries of the myocardium. He extrapolated that if the study had continued the snowball effect of attracting and accumulating more fibrin, platelets and red blood cells would cause the many more particles to reach threatening size. These emboli would then have the potential to block critical cardiac vessels or find their way into the pulmonary or cerebral circulation with potentially devastating consequences. Whelan emphasized that these findings may help to explain that, while most subacute thromboses occur three to five days post-implant, they have been reported up to 28 days

reflecting when the swelling thrombogenic mass finally reaches critical mass sufficient to clog a crucial vessel.

In 2006, Shannon reported the results of a retrospective study of postmortem cases performed on all post-angiographic neurologic complications at his medical center during the previous 5 years. He found particulate embolization present in as many as 25% of the malformations studied. Three patients developed cerebral infarctions directly attributed to the particulates deposited during cerebral angiography. Others would undoubtedly followed the same fate as their particulate "snowball-thrombi" continued to swell, but succumbed to other catastrophic events prior to critical mass or location of the growing particulate-emboli.[114] Shannon concluded that:

> "Unintentional foreign body emboli remain common in modern angiographic practice and are probably underappreciated clinically. Although such emboli are usually asymptomatic, they can be clinically devastating, and a high index of suspicion is required for diagnosis. Foreign body emboli should be included in differential diagnosis of post-angiographic ischemia or infarction."[115]

McKee identified particulate matter introduced during catheterization as the cause of several cases found with granulomas of the endocardium. In a case of mitral valve replacement on a 36 year old patient with rheumatic heart disease, a 1 cm specimen presumed to be a blood clot was recovered and sent to pathology. Histological examination revealed the mass was composed of sheets of macrophage-type cells enmeshed in a fibrin web, engorged with trapped red blood cells, all engulfing cornstarch powder particles throughout the clot.[116]

Nine days after mitral valve surgery, a 44yr old patient died when a mural thrombus enlarged sufficiently to block blood flow into the aorta. Histopathology revealed multiple mural thrombi as well as granulomatous and non-specific interstitial myocarditis involving all chambers of the heart. Thrombi were described as a collection of inflammatory cells, fibrin, platelets and red blood cells amassed around cornstarch powder particles. Cornstarch particles were also identified at the center of most of the granulomatous nodules, but not all. It was surmised that the nodules remained after the initiating foci, the powder particles, had dissolved. The cornstarch particles were identical to the powder on the gloves used in both surgery and cardiac catheterization.[117]

Verkuyl determined the deaths of three auto transfusion patients to be linked to contamination of the blood filter with glove powder prior to sterilization. The cause of death for all three patients was congestive heart failure after the blocking of pulmonary vessels with subsequent inflammatory response to the foreign presence. Rabbit inoculation with a proportionate amount of glove powder in Ringer's lactate resulted in either no reaction or acute seizure followed by death after a deepening coma within 30 minutes.[118]

Central nervous system complications: After removal of a lesion in the 4th cranial ventricle, the patient developed fever, malaise and neck stiffness. A lumbar puncture revealed clumps of polymorphonuclear leukocytes and large phagocytic cells surrounding cornstarch particles. The diagnosis was glove starch meningitis.[119]

In 1995, Green determined that glove powder with its adherent allergens can be carried into the extradural space after being deposited on the catheter by normal manipulation during insertion using powered gloves. Catheters inserted with routinely worn sterile powdered surgical gloves were observed with electron microscopy and found to be heavily contaminated. Observation of one catheter removed 26 hours after insertion revealed extensive fibrin deposition demonstrating a very reactive condition created by the powder presence. His recommendation was to use powder-free gloves.[120]

Adhesive spinal arachnoiditis is a rare condition with several potential causes, including complications of myelography. A study was conducted to determine if contamination of the cerebral spinal fluid with sterile glove powder during myelography procedures could cause this complication. Mild to severe arachnoiditis was produced in 10 of 17 animals injected with the combination of powder and Pantopaque as per normal patient procedure. Three rabbits (two injected with glove powder alone and one with both agents) died of meningitis within 1 week of injection. The combination of glove powder and Pantopaque is synergistic in producing arachnoiditis.[121]

Pain management books instruct that epidural fibrosis will occur secondary to infection, ischemia, bleeding, thrombosis, surgical sponges and glove **powder.**[122]

Thirteen days after brain surgery to remove a mass from the fourth ventricle, the patient developed fever, general malaise and neck stiffness. A lumbar puncture revealed clumps of polymorphonuclear leukocytes and large phagocytic cells surrounding round particles. The particles stained positive with periodic acid Schiff (PAS) and iodine. Under polarized light, the particles displayed Maltese-Cross birefringence. The three tests identified the core particles as cornstarch powder.[123]

Green observed what appeared to be glove powder contamination of extradural catheters after routine handling prior to use in anesthesia. No powder was noted on new catheters removed from their packaging. Two groups of catheters were prepared as per standard procedure prior to use, except that one group was handled with powdered gloves and the other group with powder-free. Under scanning electron microscope, no powder was observed to contaminate the group handled with only powder-free gloves. The catheters handled with powdered gloves revealed extensive contamination with powder. A catheter that had been handled with powdered gloves and placed in a patient prior to this realization, was removed after 26 hours of use and examined under electron microscopy. Starch particles were inside and outside the patient's catheter associated with fibrin strand activity.[124]

Ophthalmic complications: Cox reported that direct and indirect contamination of the eye with glove powder during ophthalmic surgery is thought to be one of the etiological agents in toxic lens syndrome, sterile endophthalmitis, and chronic granulomatous reactions with fibrosis and adhesion formation, as well as recurrent uveitis after cataract and intraocular lens surgery.[125]

Slit lamp photography has been used to depict the presence of birefringent refractile powder particles on the posterior intraocular lens when investigating cases of inflammation after intra-ocular lens (IOL) implant. Bene and Kranias felt the lens attracted the powder as it passed over the Sheets lens guide during insertion.[126] Powder induced inflammation has been severe enough to cause permanent

structural damage with resulting diminished visual acuity. Subsequent animal studies demonstrated a dose response corresponding with the degree of inflammation.

Stein determined that even after washing powder from gloves, his ophthalmic procedures were still plagued with powder contamination of the stromal interface with associated complications. Noting that even one powder particle was sufficient to elicit an adverse ophthalmic event, Stein felt the only solution was to use powder-free gloves. He noted that even one particle of glove powder was sufficient to elicit an adverse reaction.[127]

Orthopedic complications: Increased and prolonged inflammation with swelling and delayed healing has been associated with powder deposited during joint surgery.[128] Powder is never appropriate in orthopedic procedures where great lengths are taken to avoid particulate contamination that can cause granulomas, adhesions, chronic inflammation, osteolytis with implant loosening, opportunities for infection and biofilm formation or a potential for an indirect delayed hypersensitivity that could cause a prosthetic rejection.

Several manufacturers of implants and invasive devices have emphasized the importance of handling their products with powder-free gloves to optimize outcomes by reducing the probability or severity of possible complications including breast (ex Mentor Siltex® Smooth-Surface gel implants) and orthopedic implants (ex Swanson titanium carpal implants).

Endotoxin in clinical environment: Endotoxin present on gloves and transferred directly to patients or via glove handled catheters, instruments, implants or transplants can have devastating effects ranging from local tissue inflammation and warmth or performing the role as an adjuvant to accelerate hypersensitivity to allergens and chemical sensitizer (ex those on powder particles), to systemic complications such as fever (probable cause of many "fevers of unknown origin"), thrombus formation, disseminated intravascular coagulation, hypoglycemia, osteolysis of the bone with loosening of embedded implants,[129] multiple organ failure and shock. As described earlier, the endotoxin levels of powder slurry tanks is very often extremely high. The powder is the food source that supports the bacterial growth-the source of the endotoxin. The endotoxins are then absorbed by the cornstarch powder.

Kure experienced a rise in the number of patient fevers after cardiac catheterization. He tested the cardiac catheters after removal from the packaging and found no endotoxin. After the catheters were handled with powdered sterile gloves, the catheters were pyrogenic with varying levels of endotoxin. Rinsing the gloves with pyrogen-free water reduced endotoxin levels markedly. The incidence of febrile reactions was reduced from 11.6% to 0.6% when gloves were rinsed.[130]

Similarly, Knudsen found endotoxin transferred from gloves to catheters during cardiac catheterization procedures.[131]

Shmunes encountered post-surgical complications from endotoxin he believed was contributed by his surgical gloves. Many of the gloves he tested had endotoxin levels well over the 20EU limit placed on invasive devices and described in the United States Pharmacopeia for "Non-Pyrogenic" requirement.

One glove surface actually had 399 times the amount of endotoxin allowed on devices required to be non-pyrogenic.[132]

Because the powder slurry is the primary source of glove endotoxins and the powder serves as a means of transport, retention and slow release once implanted in the patient, powdered gloves are the primary offenders. However, even powder-free gloves can be pyrogenic if the manufacturing methods are not tightly controlled. Surgical gloves should be both powder free and low in endotoxin (non-pyrogenic). A method for testing gloves for pyrogenicity has already been established and formalized: ASTM D7102. But there is no requirement. Neither surgeon nor patient has any idea whether or not the surgical glove possesses a high level of endotoxins.

Organ procurement: Powder contamination of transplant organs and tissues whether heart, liver, kidney, cornea, cartilage, skin or any other organ or tissue during harvesting, preparation or implantation is unacceptable. All such activities should be powder-free to avoid all the complications described in this petition.[133,134]

To address this formally, The Association of periOperative Registered Nurses (AORN) developed Recommended Practices for Surgical Tissue Banking put into effect on January 1, 2006. Therein, Recommended Practice VI, number 4 states that: "Only powder-free gloves should be used. Glove powder is aerosolized when powdered gloves are used. Powder can contaminate recovered tissue and may lead to adverse reactions or rejections of the tissue."[135]

So why is this not required for non-transplant surgery?

Why are there not more recently published complications from glove powder?

- Many of the earlier studies were performed in England, and their ORs are now powder-free.
- Although we are doing a better job of tracking some of our complications than we have previously, histopathology is rarely performed on adhesions, granulomas or thrombi to identify the causative agent(s).
- Over the last 2 decades, powder studies have been focused on the ability of glove powder to absorb and disseminate NRL protein as well as on the impact that the shift to powder free has made on improved employee health (allergies, dermatitis, asthma, etc)– rather than placing this powder into the patient.

Latex allergy impacted healthcare providers: Although a decade ago, effort and some added cost were required to reduce glove protein and the powder content, the conversion and acceptance has been relatively rapid and the positive outcome for healthcare staff realized. This petition is primarily focused to accomplish the same optimal outcome for the patient.

It must be emphasized that patient symptoms are often delayed and follow-up on complications frequently handled by other healthcare professionals. Causation requires extra effort in the path lab – very rarely undertaken in this day and age of the business of healthcare. And yet the patient has no say.

The patient has no clue as to the added risk he or she is put to if the surgeon, the surgical team, circulator, Central Services staff preparing instruments and packs or individuals cleaning the OR, ER and patient rooms are wearing powdered gloves.

On performing studies and interpreting studies performed by others: Studies on the bio-reactivity of glove powder should always include powder from the glove. Otherwise, the immunological granuloma (or adhesion) pathway will be much less active as the glove manufacturing chemicals and endotoxins will not yet be present on the powder. Although even pristine ADP (glove powder before it is added to the glove) suspended in sterile physiological saline causes granulomas when injected into a surgical site, powder obtained from the glove is much more biologically reactive. The degree of inflammation, size of the granulomatous nodules, potential to invoke starch-powder granulomatous peritonitis; the persistence of any associated symptoms; and the possibility of central necrosis depends on the:

- size or amount of powder clumps or aggregates (increasing the threat perception and associated cellular defense response)
- number of previous procedures in or near the most recent surgical site
- chemicals absorbed to the powder from the glove manufacturing process
- patient's sensitivity to any of these chemicals (potentially escalating to a delayed type hypersensitivity (Type IV) reaction in addition to a foreign body response)[136]
- amount of endotoxin carried by the powder

Powder Access To The Body

Why is this petition seeking to ban glove powder from examination gloves as well as surgical gloves? To answer this question, we must identify the sources of glove powder that can find their way into the patient. Glove powder, with all its attendant contaminants from glove manufacture and "in-use pick-up", finds access into the body via a number of pathways including:

- Direct contact delivery from the surface of sterile surgical gloves into surgical wounds as:
  - loose powder from unwashed sterile gloves
  - powder aggregates or clumps from washed or wiped sterile surgical gloves
- Direct contact delivery from the surface of sterile or non-sterile gloves during wound care (surgical wounds, trauma injuries pressure or diabetic ulcers, burns, fistulas, ostomies, etc.)
- Indirect contact delivery when:
  - powdered gloves handle instruments, sponges, gauze, retractors, endoscope, sutures, irrigation basins, as well as instruments, suction yankuers, electrosurgical and electrocautery units, tubing, vascular catheters (including angio-caths) urinary and vascular catheters, guide wires, trocar/cannula assemblies, peritoneal dialysis tubing, sleeves for implant insertion including those for intraocular lenses and breast implants – all have contributed to powder-associated complications

- powdered gloves handle and manipulate orthopedic device implants, breast implants, plastic surgery implants, Penrose drains, surgical wound drains, pacemakers and wires, CVC ports
- powdered gloves handle and manipulate transplant organs and tissues during patient and cadaver harvest, preparation or transplant procedures
- powdered gloves are used in examinations resulting in migration from the point of deposition to areas where complications ensue—vaginal, rectal, oral, etc.
- powdered gloves are used to prepare devices, endoscopes, gauze packs, sponges and standard instruments followed by the set-up and wrapping of packs in Central Services
- powdered gloves are used by Environmental Services to clean patient rooms, Procedure, Cath Lab, Surgery rooms, etc.

- Fallout from airborne powder particles originating directly from gloves when donned and snapped over wrist, gown sleeves contaminated by the inside of the glove pulled over it, glove pulled off inside-out , exposing interior powder from sweaty hands teeming with microbial flora, tossed or slingshot delivered into waste, opening boxes and packages of powdered gloves, re-aerosolization of powder from previously powder-contaminated surfaces

- Inhaled "fall out" from powdered glove activities as listed above or from instruments such a endotracheal tubes, breathing circuits anesthesia equipment prepared with powdered gloves for the patients

- Addressing the healthcare provider, powder:
  - dries the skin causing irritation of many
  - carries sensitizing chemicals with the potential of sensitizing predisposed wearers or eliciting a reaction in those already sensitized by dermal contact or inhalation
  - carries NRL protein with dermal contact or inhalation
  - carries to the lungs: "fall out" from powdered glove activities can carry pathogens, chemicals, proteins, endotoxins, substances from task activities such as chemo drugs, antibiotics (potential allergens), etc.

It should be apparent that examination as well as surgical gloves must be powder-free for the sake of the patient as well as the healthcare provider.

Economic impact

Although the production of powder-free gloves involves an additional step of powder removal and an additional step of chlorination, or the incorporation of an alternative non-tacking or non-blocking agent, the volume increase and processing improvements have reduced powder-free glove prices significantly (between 30%-50%) over the last 15 years. As CMS actions are being taken to stop reimbursement for avoidable complications that occur in healthcare settings, the cost savings realized by the removal of all

powdered gloves should include that of avoided powder-associated resurgery, treatments for peritonitis, infertility reversal procedures, infections, reduced function, delayed or poor wound healing, implant replacement procedures, occupational asthma and allergic reactions or other powder-associated patient or healthcare provider complications. The avoidance of even one of each of these complications annually for a given hospital would make the conversion to powder-free a cost savings for the hospital (where the specific nosocomial complication is not CMS reimbursed); for the government (where the specific complication is CMS reimbursed); and for private insurance agencies covering the patient. Similarly, a cost savings would be realized for families that would have experienced the complications; and for our nation impacted by employee down time, lost production, lost taxable earnings and/or lost worker capabilities. Glove powder-associated morbidity and mortality is an avoidable national cost.

Environmental Impact

The removal of powder will positively impact the healthcare environment by eliminating that pervasive contaminant.

Eliminating the production of powdered gloves also favorably impacts the manufacturing environment by decreasing the deposition of powder into water or sewage systems in the event that manufacturers themselves do not have water-treatment facilities that remove the powder from effluent before release. Furthermore, the process of removing powder by washing powdered gloves followed by chlorination could adversely impact the environment if the chlorine is not properly processed prior to waste release. However, most countries appropriately have chlorine limits on effluent requiring manufacturers to treat their effluent, until chlorine levels are below specific chlorine limits prior to release.

Totally cornstarch powder-free manufacturing utilizes alternative lubricants and anti-tack solutions that never use the powder, thus favorably impacting the environment by eliminating the need to deal with the powder at all. The effluent is controlled with release limits as noted above.

Conclusion

In this day and age of complex surgeries, implants, transplants and increasingly vulnerable patients, we must address known risks. Current national efforts to protect patients and efforts at healthcare outcomes transparency, underscore that the time is now to ban medical glove powder. The list of complications associated with powder is extensive. It is not acceptable that powder is still being implanted and inhaled by unsuspecting patients.

FDA has successfully banned the use of talc and lycopodium, protecting US patients by removing the risk of associated complications. In 1997, the FDA acknowledged the adverse consequences of cross-linked cornstarch glove powder, but stated that there would be a glove shortage if powder-free were required. Since then, manufacturers have developed new processes and expanded their powder-free capacity. There will not be a shortage as long as there is sufficient time to work through inventory and work with hospitals. Glove powder-associated complications have continued to be reported since then, and

studies continue to provide new insights into glove powder pathogenesis. Yet the complications continue. It is time for our healthcare facilities to be powder-free.

Certification: The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

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EXHIBIT C

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Evaluation of Powdered Latex Medical Gloves Using ASTM D6124-00

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Abstract

Natural rubber latex proteins are recognized as a cause of Type I (Immediate Type Hypersensitivity) reaction in some individuals who have been exposed to latex devices. Residual former-release, stripping, and/or donning powders have been found to carry these allergenic proteins into the air during handling and use. Exposure to airborne glove powder contaminated with latex allergens is known to provoke respiratory allergic symptoms in latex-sensitized individuals and may make it difficult for these individuals to continue working in jobs involving such exposure. The Food and Drug Administration has proposed a maximum level of 120 mg of donning powder/particulates per glove on powdered gloves. A survey was conducted to determine current powder levels on commercially available powdered latex patient examination gloves and surgeons' gloves. Ninety-seven samples of powdered latex medical gloves representing 32 different brands produced by foreign and domestic manufacturers for the U.S. market were evaluated for residual powders per glove by ASTM D 6124-00, Standard Test Method for Residual Powder on Medical Gloves. Powder levels ranged from 37 to 260 mg per glove for patient examination gloves and 30 to 513 mg per glove for surgeons' gloves. Of the gloves tested, 55.7% met the new maximum powder guidelines.

Keywords:
ASTM D 6124, health care services, health care workers, latex allergy, maximum powder limits, powdered medical gloves

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